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Clinicopathological case: progressive somnolence and dementia in an accountant

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Abstract

A 63-year-old accountant developed progressive somnolence, cognitive decline, gait disturbance and cerebellar dysfunction with autonomic features. This report documents the clinicopathological conference at the 39th Edinburgh Advanced Neurology Course 2017.

History

A 63-year-old right-handed accountant became unwell in summer 2013, with abdominal symptoms, somnolence, unsteadiness and weight loss of two stones. He had stopped driving due to safety concerns; he had become withdrawn, lost enjoyment playing guitar, had reduced libido and had become reluctant to leave the house. He was taking omeprazole and fluoxetine. He had previously undergone mastoid surgery. He lived with his wife and daughter, had never smoked and drank little alcohol. He had completed a 400-mile bike trip in India in 2011 (Figure 1A). His mother and maternal grandmother had dementia in their 80s. Initial examination showed square wave jerks, unsteady gait and finger-nose ataxia, worse on the left. An Addenbrooke's Cognitive Examination-Revised (ACE-R) score was 99/100.

He was diagnosed with sleep apnoea, and initially responded well to continuous positive airway pressure (CPAP), but by mid-2015 was sleeping up to 20 hours/day. His unsteadiness progressed, he developed generalised itch and became apathetic. He made inappropriate jokes, and lost empathy. He developed anxiety and a marked fear of heights, urinary hesitancy and erectile dysfunction, and struggled to operate the TV remote control. He suffered from acid reflux and diarrhoea.

On examination (in July 2015), there were bilateral palmomental, snout and pout reflexes, jerky saccades with nystagmus and slurred speech. There was no bradykinesia, but he showed a staring appearance. Tone and muscle strength were normal, and his gait was broad based. There was difficulty with praxis and sequencing. His plantar flexors and tendon reflexes were normal. His investigations were unremarkable (Box1), except for atrophy on MR scan of brain, and cerebrospinal fluid (CSF) showed $7 \times 10^9/L$ white cells and unmatched oligoclonal bands (see results). Prednisolone 40 mg for 1 month gave no benefit. By March 2016, he was using a wheelchair. His ACE-R was 69/100 (attention 16/18, memory 16/26, fluency 3/14, language 23/26, visuospatial 7/16). He had reduced facial expression, increased tone in all limbs and prominent cerebellar signs. In April 2016, he was admitted to hospital after a fall, discharged to a nursing home (Figure 1B) and, by October 2016, he was bed bound. He died in November 2016 aged 66 years.

Box 1

Investigations

Blood

- Full blood count, erythrocyte sedimentation rate, plasma glucose, liver function tests, thyroid function tests, serum urea, electrolytes, creatinine and creatine kinase were all normal.

- Vitamin E 5.3 $\mu\text{mol}/\text{mmol}$ (normal).
- Serum lipids and triglycerides were normal.
- Antibodies to voltage-gated potassium channels, voltage-gated calcium channels, glutamic acid decarboxylase, islet antigen-2, N-methyl-D-aspartate (NMDA), thyroperoxidase, acetylcholine receptors, Yo, Hu and Ri, tissue transglutaminase IgA were all negative.
- Extractable nuclear antigens, antinuclear antibodies, anti-cyclic citrullinated peptide were negative.
- HIV and antitreponemal IgG were negative.
- Ataxia genetics: *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *FRDA* and *FXTA* genes were all negative.
- Neurodegenerative gene panel: C9orf72 5–10 repeats (normal) both alleles, *APP*, *CHMP2B*, *FUS*, *GRN*, *LRRK2*, *MAPT*, *PARK2*, *PSEN1*, *PSEN2*, *SOD1*, *SQSTM1*, *TARDBP*, *UBQLN2*, *VAPB*, *VCP* sequences were all normal.

CSF

- March 2014: white cell count $6 \times 10^9/\text{L}$; red cell count $0 \times 10^{12}/\text{L}$; CSF glucose 3.3 (serum 4.1), protein 0.31 g/L; multiple unpaired IgG oligoclonal bands in CSF.
- September 2015: white cell count $7 \times 10^9/\text{L}$; red cell count $0 \times 10^{12}/\text{L}$; CSF glucose 3.7 (serum 4.5), protein 0.33 g/L; multiple unpaired oligoclonal bands in CSF; tau 111, β -amyloid 104 (normal), Whipple's PCR negative; CSF microscopy no organisms seen; enterovirus, HSV1 PCR, HSV2 PCR, parechovirus PCR, varicella zoster PCR all negative; CSF cytology (4 mL) no significant cellular component, no evidence of malignancy or inflammation.

Imaging

- March 2014: MR scan of brain showed generalised atrophy, advanced for age, no other abnormalities.
- January 2015: MR scan of brain (unenhanced) showed moderate global cerebral atrophy, advanced for age, unchanged from 2014. Mild chronic microvascular changes also accelerated for age. No other abnormalities.
- June 2014: dopamine transporter scan (DaTSCAN) was normal.
- September 2015: CT scan of chest/abdomen/pelvis with contrast was unremarkable.

EEG

- 2015: bursts of generalised slow with some intermixed sharp waves; in keeping with cerebral dysfunction but not specific.

Sleep study

- May 2014: 55 apnoeas/hypopnoeas per hour.

Colonoscopy

- Two polyps removed from proximal ascending colon: tubular adenoma showing low-grade dysplasia. Pedunculated polyp in splenic flexure: tubular adenoma, no sign of invasion. Two biopsies of right and left colon: normal.

Upper GI endoscopy

- Prepyloric biopsies: chemical gastritis; duodenal D2 biopsies: mild duodenitis.
- APP, amyloid precursor protein; CHMP2B, charged multivesicular body protein 2B; CSF, cerebrospinal fluid; EEG, electroencephalogram; FRDA, Friedreich ataxia; FUS, fused in sarcoma; FXTA, fragile X tremor associated; GI, gastrointestinal; GRN, progranulin gene; HSV, herpes simplex virus; LRRK2, leucine-rich repeat kinase 2; MAPT, microtubule-associated protein tau; PARK2, gene-encoding Parkin; PSEN, gene-encoding presenilin; SCA, spinocerebellar ataxia; SOD1, superoxide dismutase 1; SQSTM1, gene-encoding sequestosome 1; TARDBP, gene for TDP-43 (Tar-binding protein 43); UBQLN2, gene for ubiquilin-2; VAPB, gene for vesicle-associated membrane protein B/C; VCP, valosin-containing protein.

Discussant: Professor Jonathon Schott

The received wisdom in medicine—and neurology in particular—is that diagnosis is almost always made from the history. Evidence comes from a study that looked at outpatient clinics across a spectrum of disciplines, including neurology, and determined the contribution that the history, examination and investigations made to the final diagnosis. History accounted for 82% of diagnoses, 9% came from the examination and investigations helped in 9% (1). In a CPC, the investigation findings are unlikely to give the answer, and so reviewing the history is even more important.

The history...

He is an educated man, important when it comes to assessing cognition. He takes omeprazole and fluoxetine, both commonly prescribed drugs but potentially relevant if gastrointestinal symptoms or depression are part of his neurological illness. He has vague abdominal symptoms, which hint at an autonomic problem. He completed a bike trip in India in 2011, meaning balance and planning skills were good then, but might he have been exposed to infection? His mother developed dementia in late life, not unusual and unlikely to be relevant.

A prominent early feature was daytime somnolence. He was struggling with work, which may reflect sleepiness, depression or cognitive problems. He was diagnosed with obstructive sleep apnoea and initially responded well to CPAP. However, the degree of his somnolence—sleeping 20 hours/day—and the subsequent course make it clear this is not just sleep apnoea. One year into his illness he is unsteady, which could reflect vestibular dysfunction, neuropathy or pyramidal weakness, but he has a broad-based unsteady gait, square wave jerks, with minimal finger-nose ataxia, suggesting an axial cerebellar problem. Importantly, he is not parkinsonian. He has poor spatial awareness but it is not clear whether this is due to a visuospatial problem (right parietal dysfunction), sleepiness or executive dysfunction. He has lost two stones in weight, which might reflect a systemic illness or autonomic dysfunction.

He becomes apathetic, likely reflecting decline in executive function. He has difficulty using the TV remote control, which may reflect dyspraxia (left parietal dysfunction), visuospatial (right parietal lobe) or executive problems. Neuropsychiatric features also emerge (anxiety). He develops itch, which is most often due to diseases such as eczema or psoriasis, but can suggest systemic disorders including lymphoma and leukaemia. There are neurological causes for 'central' itch, including anti-aquaporin-4 syndromes. His itch is worse at night, commonly the case because of a lack of distraction, but with sleep disturbance raises the possibility of a primary parasomnia (2). Latterly, he develops clear autonomic disturbance, with urinary hesitancy, erectile dysfunction, reflux and loose stools.

...and the examination

The palmomental reflex is not a useful diagnostic sign (3). He has a snout reflex, a frontal release sign. Tone, power and reflexes are normal, but he has a pout reflex, an upper motor neurone sign. He has jerky saccades with nystagmus, localising pathology to the cerebellum, brainstem or connections; there is slurring of speech suggesting the former. Despite a staring appearance he is not bradykinetic, that is, he does not have true parkinsonism. He has difficulty with praxis, consistent with left parietal dysfunction.

Three years later he is a wheelchair user, hypomimic, with increased tone throughout. He has marked cerebellar signs and memory problems. We must exercise caution when considering memory as a localising feature in the context of excessive sleepiness and dysexecutive function where it is difficult to maintain concentration. The breakdown of his ACE-R score reveals that fluency is very affected (a frontal/executive feature) as is visuospatial functioning, while language and attention are relatively spared. His memory is impaired although not as much as other domains. This pattern can therefore best be described as a frontoparietal syndrome.

Contribution of investigations

Routine bloods, microbiology and basic antibodies provide no further diagnostic information. Imaging shows no significant white matter disease, mitigating against a vascular or conventional

(eg, demyelinating) inflammatory process. Diffusion imaging provides no support for recent stroke or prion disease. There is atrophy affecting the posterior frontal lobe and the anterior parietal lobes but not the hippocampi, and there is progression (atrophy) between the studies. This is an unusual pattern, and would not be typical for the frontotemporal dementia (FTD) syndromes, or Alzheimer's disease (AD). There is a hint of midbrain and cerebellar atrophy, which might suggest an atypical parkinsonian syndrome (progressive supranuclear palsy or multiple system atrophy) but the history would be atypical for either, and the dopamine transporter (DAT) scan is negative.

He has two CSF examinations, both abnormal, with a mildly elevated cell count and unpaired oligoclonal bands on each occasion. He has had various negative genetic tests. Serum voltage-gated potassium channel complex antibodies were negative; we would now test for specific antibody subtypes, but this syndrome does not fit with LGI-1 or CASPR2 antibody-associated encephalitis. Stiff-person syndrome is worth considering, but anti-glutamic acid decarboxylase antibodies are negative; antiglycine antibodies were presumably not available for testing at the time. Antineuronal antibodies were negative, although that a limited panel was reported. Further CSF studies included concentrations of tau and A β 1–42. Tau is elevated in AD and often extremely elevated in prion disease, but was normal in this case. While a normal range for A β 1–42 is not provided, the assay usually employed in the UK has a normal range of ~550–650 pM/L, lower concentrations being abnormal. An A β 1–42 of 104 in this case is *very* low, and perhaps more reflective of a handling/storage error than indicating brain β -amyloid deposition alone; in any case, the profile does not suggest AD. For the purposes of a CPC, it is important that Whipple's PCR was negative. The sensitivity and specificity of the real-time quaking-induced conversion (RT-QuIC) test is extremely high for prion disease (4), and the normal concentration in this case strongly mitigates against this diagnosis, and sporadic Creutzfeldt-Jakob disease in particular.

CT scans of chest, abdomen and pelvis were normal, reducing the likelihood of an occult tumour causing a paraneoplastic process, or sarcoidosis. The electroencephalogram was non-specific. The normal colonoscopy and endoscopy reinforce the clinical impression that his gastrointestinal symptoms are likely autonomic.

Several investigations have not been performed: there is no MR scan of spinal cord, and no contrast MR scan of brain. Whole-body fluorodeoxyglucose-positron emission tomography, sensitive for detecting occult neoplasia, was not performed. There is no peripheral electrophysiology. Importantly, and as sleep impairment is such a dominant part of his presentation, the information from the sleep study is limited. He had 55 apnoeas and hypopnoeas per hour, putting him in the very severe category for sleep apnoea (severe >30 per hour). We do not know if he had rapid eye movement (REM) sleep behavioural disturbance which is seen in Lewy body diseases, but also in some autoimmune syndromes. We do not know if there is agrypnia excitata (complete loss of slow wave sleep with sustained autonomic activity), which limits the differential diagnosis to only a few conditions, such as Morvan's syndrome, fatal familial insomnia or delirium tremens.

In conclusion

He is a 63-year-old man, with a 3-year history of a progressive fatal illness. Relevant findings are of early and prominent daytime somnolence, cognitive impairment with dysexecutive and parietal features, and gait disturbance. There is evidence for cerebellar or brainstem/cerebellar disconnection syndrome, with autonomic features. There is non-specific brain atrophy and an active CSF. The softer symptoms and signs include hints of an extrapyramidal disorder without parkinsonism, itch and weight loss. There was no response to modest immune suppression.

Refining the diagnosis

When faced with a difficult case, it is useful to go back to first principles and apply a 'surgical sieve' (Box 2). There is no evidence for a primary brain tumour but this does not exclude other malignancies, for example, intravascular lymphoma. A paraneoplastic syndrome cannot be excluded on current evidence but the history is relatively long. There are no 'classical'

paraneoplastic antibodies, the caveat being that antibody testing and whole-body imaging were limited. His trip to India notwithstanding, there is no evidence for infection, for which the history would be long; imaging, HIV and treponemal serology were normal or negative. There are strong hints towards an immune process with an elevated CSF cell count and multiple central nervous system-specific bands. He did not respond to immunosuppression, although this was only a modest attempt, and not all autoimmune or inflammatory conditions respond to treatment. Degenerative causes are possible, with some soft signs suggestive of atypical parkinsonism, although the clinical features do not fit easily with any one of the classical syndromes, and the DAT scan was normal. Prion disease would, I think, be unlikely with the normal diffusion-weighted MRI, negative RT-QuIC and active CSF. I think that trauma, metabolic and endocrine causes can safely be excluded.

Box 2

The surgical sieve with possible causes highlighted

- Tumour/paraneoplastic
- Trauma
- Infection
- Infarction
- Immunological
- Metabolic
- Endocrine
- Degenerative (including genetic)
- Haematological

There are two central features that one has to explain to solve this case: the profound somnolence and the active CSF.

Many causes of somnolence can be excluded from the history, for example, narcolepsy, obstructive sleep apnoea, central hypoventilation and restless legs syndrome. There are several congenital syndromes with profound somnolence (Kleine-Levin, Prader-Willi, Coffin-Lowry), which clearly are not relevant. There were no hypothalamic lesions on the (unenhanced) imaging; some causes (eg, lymphoma) may not be seen. Degenerative causes such as Niemann-Pick disease type C can give rise to somnolence with eye movement abnormalities and cerebellar dysfunction, but there is no splenomegaly and the active CSF would not fit. Conventional neurodegenerative disorders (AD, FTD and the parkinsonian syndromes) and prion disease, all of which can cause sleep impairment, are I think excluded. Sarcoidosis would be unusual without white matter imaging changes. Paraneoplastic and autoimmune conditions associated with CASPR2 and LGI-1 can cause REM sleep behaviour disorder and agrypnia. N-methyl-D-aspartate antibodies were not done on the CSF but were negative in the serum. Aquaporin-4 antibodies have been detected in narcolepsy but the history does not fit, and there are no imaging changes to suggest this diagnosis. Bickerstaff's encephalitis can be associated with sleep disturbance; we do not know whether anti-GQ1b antibodies were present, but this would be a very long and indolent history. Finally, there is IgLON5 antibody syndrome, a relatively new autoimmune condition associated with prominent sleep disturbance.

Of the above conditions, only a few would usually be associated with an active CSF: illnesses associated with hypothalamic invasion potentially could, as could paraneoplasia, sarcoidosis and the autoimmune conditions. Narrowing down the differential to the three most likely conditions on this basis leads me to suggest paraneoplasia, lymphoma and IgLON5. Table 1 provides information on these conditions and their associations with the core clinical features in this case.

	Paraneoplastic	Lymphoma	IgLON5
Somnolence	+/-	+/-	++

Cognitive	+	+	+
Gait	+/-	+/-	++
Cerebellar	++	+/-	+
Autonomic	+	+	++
Normal imaging	+/-	+/-	++
Cellular CSF	+	+	+/-
OCBs	+/-	+/-	+/-

Table 2, Clinical features present in the patient, and the frequency with which they are observed in paraneoplastic conditions, lymphoma and IgLON5 cases

Conclusion and final diagnosis

I think the best fit would be an IgLON5 antibody syndrome. The first case series of patients with IgLON5 antibodies was described a few years ago from a sleep laboratory, and several cases have since been described, with two larger case series published recently (5, 6). IgLON5 is a neuronal cell adhesion molecule of unknown function. Honorat *et al* described 20 cases, with a median onset of 62 years, with insidious onset of sleep-disordered breathing and parasomnia, gait instability, abnormal eye movements, dysphagia, respiratory dysfunction, ataxia, dystonia, dysarthria, cognitive dysfunction, dysautonomia (bladder function, gut motility, thermoregulation, orthostatic intolerance) and normal MR scan of brain. In contrast to this case, the CSF was typically non-inflammatory, but was in some. The second case series from the Mayo Clinic reported 22 patients, median onset 64 years of age, where the initial problem was with sleep in one-third, gait problems in a further third, bulbar dysfunction in 14%, chorea in 9% and cognitive decline in 5%. They describe four subtypes: a sleep disorder with parasomnia and sleep breathing difficulty; a bulbar syndrome; a progressive supranuclear palsy-like syndrome; and a syndrome associated with cognitive decline with or without chorea. All developed parasomnia, sleep apnoea, insomnia or excess sleepiness, and there was a strong association with *HLA-DRB1*10:001* and *HLA-DQB1*0501*. The cases had often been diagnosed as atypical multiple system atrophy or atypical progressive supranuclear palsy. IgLON5 cases also have an intriguing link between autoimmunity and neurodegeneration, with the pathology showing three-repeat (3R) and four-repeat (4R) tau, without evidence of inflammation, in the basal ganglia, the hypothalamus and other regions accounting for the specific symptoms, and there are now pathological criteria described.

While I have never diagnosed a case previously and so do so with trepidation, my suggestion is that the patient had anti-IgLON5 disease, and that pathology will show subcortical deposition of 3R and 4R tau.

Questions from the audience (part 1)

Jon Stone [JXXXS]: He was my patient and neighbour of my sister in law, so I knew him before he became unwell. His family commented that previously he was a chronic *insomniac*, so hypersomnia was a significant change.

Suvankar Pal [SP]: He passed through my memory clinic. I remember feeling anxious about his CSF cell count, and it was about this time that he had the treatment with steroids.

JS: Did you consider more intensive immune suppression?

JXXXS: He deteriorated so rapidly that we agreed with the family it was not worthwhile pursuing.

JS: If it were IgLON5, the evidence seems to be that patients do not typically respond to immunosuppression in any case.

Audience member: With the profound weight loss, gastrointestinal symptoms, do you think anti-DPPX (anti dipeptidyl-peptidase-like protein 6) syndrome might be a possibility?

JS: I have not seen a case of DPPX antibody-associated encephalitis but the typical triad is of cognitive decline, diarrhoea and gastro-intestinal disturbance and central nervous system hyper-

excitability rather than sleepiness. Having seen how the phenotype of new autoimmune conditions can expand over time, I would however not exclude this as a possibility.

Alison Green [AG]: Do you know if there are reports of CSF phosphorylated tau being elevated in IgLON5?

JS: We know that CSF tau is often not elevated in a number of primary tauopathies (eg, progressive supranuclear palsy), but I do not know if this has been established in IgLON5.

AG: We found that of the CSF samples of patients with Creutzfeldt-Jakob disease, 1% are associated with moderately elevated white cell counts, such as 7 or so. Once you get to 20 white cells then it becomes very unlikely.

Pathology

The brain was within normal limits, weighing 1364 g. The cerebrum showed no obvious atrophy, and on sectioning there were no macroscopic focal lesions in cortical grey matter, white matter or deep grey matter. The main pathology was related to the cerebellum, which showed striking atrophy, predominantly involving the vermis and the medial parts of the hemispheres bilaterally. Histological assessment of brain sections confirmed cerebellar pathology. Within the cerebellar cortex there were areas of clear damage, with degenerating Purkinje cells and torpedoes (fusiform swellings of Purkinje cell axons within the granular layer). The initial immunohistochemical assessment of proteins associated with neurodegeneration was undertaken, assessing tau, β -amyloid and α -synuclein.

There were occasional neurofibrillary tangles identified by tau immunohistochemistry but limited to the entorhinal cortex, with a few β -amyloid immunoreactive diffuse plaques. Further immunohistochemistry showed no deposition of abnormal prion protein, TDP43, ubiquitin or fused in sarcoma (FUS).

At this stage the pathological conclusions were as follows:

- Focal cerebellar atrophy.
- Tau pathology Braak stage 1.
- β -amyloid plaque Thal phase 1.
-

In addition, there was no inflammation excluding an encephalitic process, and no evidence of any neoplastic process. From a prion perspective, he was part of a study that included detailed biochemical and histochemical assessment, and this was negative.

When considering a neurodegenerative disorder, we go through the following processes. We assess extracellular and intracellular abnormal protein accumulation. Extracellular accumulation is mainly amyloid, with parenchymal and vascular forms, and with this we may see an associated vasculitis. We then move through the intracellular proteins that can accumulate including tauopathies, synucleinopathies, TDP-43 proteinopathies, FUS and polyQ (trinucleotide repeat) disorders. The mix of proteins and the pattern of protein distribution (neuronal, glial, mixed) helps determine the more precise pathological diagnosis.

Pathologists use the same diagnostic process as clinicians; starting with a wide range of differentials suggested by the clinical presentation aligned with histopathological and immunohistochemical assessment, until we arrive at a final diagnosis. Thus, in this case, the important negatives are: there was no neoplastic process, including gliomatosis, and no intravascular lymphoma; there was no metabolic encephalitic process, and no inflammatory processes, including those described for paraneoplastic conditions. We then consider neurodegenerative conditions. With regard to extracellular protein deposition we have excluded a prionopathy, and we have no evidence of any amyloid disorders, such as β -amyloid deposition or the rare familial amyloidoses. We then consider intracellular proteinopathies; there was no glial tau deposition and very limited neuronal expression of tau. There was no tau deposition in the hypothalamus or tegmentum of the brainstem as has previously been described in IgLON5 cases. There was no abnormal deposition of α -synuclein, TDP-43, FUS, and no evidence of

neuroserpin disorders or neuroferritinopathies. We did see polyglutamine accumulation in the vermis in the Purkinje cells. However, it is not the typical distribution one would expect for a trinucleotide repeat disorder, where nuclear accumulation is typically described. Cytoplasmic accumulation is described but not in the absence of a nuclear component. There was also no colocalisation with ubiquitin, which is typical of trinucleotide repeat disorders. However, the polyQ accumulation was considered to be pathological deposition in the cytoplasm of Purkinje cells, and minimal amounts in cortical neurones. Given the clinical scenario, I wondered about SCA17. There is a single postmortem report that describes polyQ accumulation although it was predominantly nuclear.

The bottom line, following detailed postmortem examination, is we do not have a definitive pathological diagnosis.

Questions and comments from the (stunned and now silent) audience (part 2)

RJD: You're thinking why on earth choose this for a CPC—a case with no answer? Well this is real life, we wondered if more analysis during a CPC might lead to a diagnosis. We now have a clinical diagnosis and a pathological diagnosis (sort of), which are different.

JS: Given the extent of the symptoms and signs, the absence of much in the way of neuropathological findings and of a definite diagnosis is surprising. What little there is to go on suggests cerebellar pathology. The possibility of SCA-17 was raised—this is typically considered as a differential diagnosis of Huntington's disease, and whilst it can be associated with a broader and variable clinical phenotype, I do not think this would easily explain some of the allied details, such as active CSF, and prominent drowsiness.

JXXS: It's disappointing you didn't find [pathological] atrophy, to match with the MRI scans.

What were we looking at with the MRI? He also appeared to have parietal signs, so are we just appearing to see what we want to see? I'm assuming that pathology is the gold standard.

Colin Smith: I think it's the resolution of the naked eye looking at brain sections as opposed to the resolution of MRI, especially where you can look at things sequentially. Certainly though, the brain weight was within normal limits, and the atrophy cannot have been terribly significant if not present to the naked eye.

Further testing

Post-CPC testing for IgLON5 antibodies and SCA17 genetics were negative. Rather than wrapping this case up with a neat final diagnosis, this allows us to highlight a number of learning points. A precise diagnosis can elude highly experienced neurologists, even with the assistance of postmortem data. The patient had a rich array of symptoms to help localisation and diagnosis. Some of these signs had their own difficulties in interpretation though, such as appearing superficially parkinsonian, but without parkinsonism. The case highlighted how fresh eyes can also uncover new possibilities: SCA-17 and IgLON5 were not considered before this CPC. Partly this is because for IgLON5 the antibody and syndrome were only characterised in 2014 (7). Professor Schott discussed the fast-evolving world of antibodies associated with autoimmune and paraneoplastic encephalopathies. Surrogate markers such as thyroid peroxidase or intracellular targets such as Ri, Yo and Hu are giving way to more specific antigenic targets. The field has evolved through the refinement of voltage-gated potassium channel complex antibodies to CASPR2 and LGI-1, to an explosion of overlapping syndromes associated with cell surface antibodies against GABA-A, GABA-B, glycine, AMPA, mGluR5, mGluR1, Homer-3, DNER and DPPX, to name a few (8). It would be naïve to believe there are no further syndromes and antibodies awaiting identification. Similarly, the molecular and genetic basis of neurodegeneration continues to expand, for example, the spinocerebellar ataxias. In addition, the testing for these conditions advances, as single gene testing moves towards panels, and inevitably with time towards whole exome and genome sequencing.

This case demonstrated an expert's way of working to refine the diagnosis, which is the true value of a CPC, the ultimate teaching resource. Professor Schott approached the case from several angles. He focused on the history to identify the cause and to localise the problems. His focus on

the extensive investigation results was to identify the few key results. This working enabled him to hone in on three key possibilities: two autoimmune processes (paraneoplasia and IgLON5) or lymphoma. The pathology excluded lymphoma, but what of the two autoimmune processes? Paraneoplastic conditions are associated with a wide array of pathology depending on the underlying condition. Paraneoplastic cerebellar degeneration (PCD) is the most common central paraneoplastic syndrome. Even among cases of PCD though there is heterogeneity in terms of location of damage, but also pathological changes. Some cases are purely degenerative, with loss of Purkinje and basket cells, and thinning of the molecular layer. In these cases, the deep grey nuclei are spared. Some patients with PCD have inflammatory changes, with reactive astrocytes and inflammation of the overlying leptomeninges (9). Some patients with PCD have cell loss within the corticospinal, spinocerebellar and dorsal column tracts, whereas in others it is confined to the cerebellum. Whether this heterogeneity is related to the associated antibody is unknown: PCD has been found associated with Yo, Hu, Ri, P/Q-voltage-gated calcium channel, CRMP5, Ma and Zic4 antibodies (8). The lack of a whole-body postmortem means that a distant malignancy cannot be excluded.

There are proposed pathological criteria for IgLON5 disease (10). The brains of six patients were examined and found to have very similar neurodegenerative features with accumulation of 3R and 4R tau in a rostrocaudal gradient of severity. The areas with highest density were the hypothalamus, brainstem tegmentum, pons and medulla. The distribution of tau mimics that of progressive supranuclear palsy, but is absent from the basal ganglia and supratentorial regions. In addition to the characteristic neurodegeneration, IgLON5 disease is also associated with *HLA-DRB1*1001* and *HLA-DQB1*0501* haplotypes in all tested cases. Postmortem antibody testing appears to have excluded this diagnosis, although which autoimmune disorder does not include an 'antibody-negative' subsection?

It is unusual and unexpected to have CPC without a pathological diagnosis. It is difficult to know the prevalence of progressive, fatal neurological disorders with unenlightening postmortem pathology. However, there are case series of brain biopsies in the diagnosis of various neurodegenerative and inflammatory conditions. Warren *et al* (11) performed a retrospective analysis of 90 biopsies taken to investigate of dementia between 1989 and 2003 at the National Hospital for Neurology and Neurosurgery, London, UK. This was predominantly in younger cases where there was felt to be the possibility of a reversible cause. One of these biopsies was reported as normal, and 33 showed non-specific gliosis. The biopsies were predominantly full thickness resections of leptomeninges, cortex and white matter from the non-dominant frontal lobe. Unfortunately, most of these cases were lost to follow-up subsequently but 10 patients in the study had postmortems. Six of these had non-specific biopsy findings, and postmortems were diagnosed as Creutzfeldt-Jakob disease (three cases), multiple sclerosis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and, finally, suggestion of a mitochondrial cytopathy. Biopsy is much more likely to miss focal inflammatory or neurodegenerative pathology. If a patient with IgLON5 had a non-dominant frontal lobe biopsy it would be expected to appear either normal or non-diagnostic based on the six cases described (10). The CPC discussant was the first author on a follow-up study to Warren *et al*'s biopsy study, looking at brain biopsies between 2004 and 2009 at the same institute. This identified 19 cases, and the biopsy was diagnostic in 74%. Of the non-diagnostic biopsies, four had non-specific gliosis or non-specific chronic inflammation, one extensive cortical necrosis and none were normal.

This case has been educational into the role of generating a differential diagnosis, as well as an overview of IgLON5 disease and its associated pathology. However, the case still lacks a final diagnosis, and in the spirit of collaboration we open this up to readers for further suggestions.

Key points

- Prominent neurological symptoms and signs may not reflect structural abnormalities picked up either by imaging or by pathology.
- Autopsy does not always provide the diagnosis.
- There has been a recent explosion in the number of paraneoplastic antibody associated syndromes, but for most the pathological findings are unknown.

- IgLON5 is a recently described paraneoplastic syndrome associated with prominent sleep disorder.

References

- (1) Hampton JR, Harrison MJ, Mitchell JR, *et al* Relative contributions of history-taking, physical examination, and laboratory investigation to diagnosis and management of medical outpatients. *Br Med J* 1975;**2**:486–9
- (2) Nigam G, Riaz M, Hershner SD, *et al*. Sleep Related Scratching: A Distinct Parasomnia? *J Clin Sleep Med* 2016;**12**:139–42
- (3) Schott JM, Rossor MN. The palmomental reflex: stop scratching around!. *Pract Neurol* 2016;**16**:500–1
- (4) Peden AH, McGuire LI, Appleford NE, *et al*. Sensitive and specific detection of sporadic Creutzfeldt-Jakob disease brain prion protein using real-time quaking-induced conversion. *J Gen Virol* 2012;**93**:438–49
- (5) Honorat JA, Komorowski L, Josephs KA, *et al*. IgLON5 antibody: Neurological accompaniments and outcomes in 20 patients. *Neurol Neuroimmunol Neuroinflamm* 2017;**4**:e385
- (6) Gaig C, Graus F, Compta Y, *et al*. Clinical manifestations of the anti-IgLON5 disease. *Neurology* 2017;**88**:1736–43
- (7) Sabater L, Gaig C, Gelpi E, *et al*. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol* 2014;**13**:575–86
- (8) Lancaster E. Paraneoplastic Disorders. *Continuum* 2017;**23**:1653–79
- (9) Scaravilli F, An SF, Groves M, *et al*. The neuropathology of paraneoplastic syndromes. *Brain Pathol* 1999;**9**:251–60
- (10) Gelpi E, Höftberger R, Graus F, *et al*. Neuropathological criteria of anti-IgLON5-related tauopathy. *Acta Neuropathol* 2016;**132**:531–43
- (11) Warren JD, Schott JM, Fox NC, *et al*. Brain biopsy in dementia. *Brain* 2005;**128**:2016–25.